First-in-Human Dose Escalation of Monalizumab Plus Durvalumab With Expansion in Patients With Metastatic Microsatellite-Stable Colorectal Cancer

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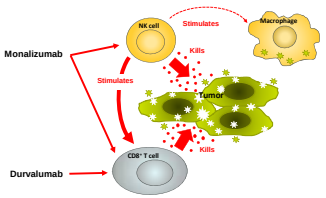
Abstract #3540

Background

- Tumor-infiltrating natural killer (NK) cells and CD8+ T cells are enriched with CD94/NKG2A and/or PD-1 in several cancer types, and HLA-E is overexpressed in several solid tumors[1]
- Monalizumab (IPH2201) is a humanized immunoglobulin (IgG) 4 monoclonal antibody that targets NKG2A, blocking binding to its receptor HLA-E, which results in suppression of inhibitory signaling by tumors on NK cells and tumor-infiltrating CD8+ T cells[2]
- Durvalumab is a human IgG1κ monoclonal antibody that blocks programmed death ligand-1 (PD-L1) binding to programmed death-1 (PD-1) and CD80 receptors, which enables T cells to recognize and kill tumor cells[3]
- Blocking non-redundant NKG2A/HLA-E and PD-1/PD-L1 checkpoint pathways with the combination of monalizumab and durvalumab could enhance responses of NK and CD8+ T cells present in close proximity to tumor cells, thereby boosting innate and adaptive immunity (**Figure 1**)[4]
- Metastatic microsatellite-stable colorectal cancer (MSS-CRC) has been historically nonresponsive to single-agent anti-PD-1/PD-L1 therapy[4]; immunotherapy combinations may stimulate an immune response in MSS-CRC
- This first-in-human phase I study evaluated monalizumab plus durvalumab in patients with select advanced solid tumors; with expansion in MSS-CRC

Figure 1. Mechanism of Action of Monalizumab and Durvalumab



METHODS

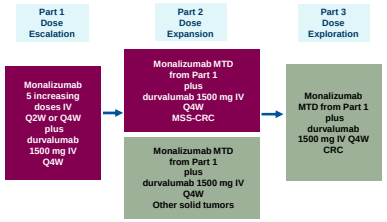
Key Inclusion/Exclusion Criteria

- Histologic documentation of advanced recurrent or metastatic cancer
  - For the dose expansion phase, eligible patients had metastatic MSS-CRC, with documented mutation test during screening indicating no defective DNA mismatch repair
- Must have received 1–3 prior lines of standard systemic therapy in the recurrent/metastatic setting
- No prior treatment with immunotherapy agents
- ≥1 lesion measurable by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Adequate hematologic, hepatic, and renal function

Study Design

- This phase I, multicenter, open-label study (NCT02671435) consists of 3 parts (**Figure 2**)
  - Part 1: Dose escalation of monalizumab/durvalumab in patients with select solid tumors
  - Part 2: Dose expansion of monalizumab/ durvalumab in select advanced solid tumors, including MSS-CRC
  - Part 3: Dose exploration of monalizumab/durvalumab in combination with standard of care therapies in patients with CRC
- Data reported here are as of April 23, 2018
- We report on Parts 1 and 2

Figure 2. Study Design and Treatment



IV, intravenous; MTD, maximum tolerated dose; Q2W, every 2 weeks; Q4W, every 4 weeks.

- Treatment continued until unacceptable toxicity, confirmed progressive disease, or withdrawal for another reason

RESULTS

Patients

- A total of 15 patients were enrolled in the dose escalation phase, and 40 MSS-CRC patients were enrolled in the dose expansion phase
- For the MSS-CRC expansion cohort:
  - 35 (87.5%) patients had ≥2 prior lines of therapy for recurrent/metastatic disease
  - 32 (80.0%) patients discontinued treatment because of progressive disease
  - Median duration of follow-up was 6.6 months (0.3–14.0)
- Patient demographic and baseline disease characteristics of all enrolled patients are shown in **Table 1**

Table 1. Patient Demographic and Baseline Disease Characteristics

Parameter	Total Escalation (n=15)	MSS-CRC Expansion (n=40)
Median age (range), y	69 (33–76)	55 (23–79)
Male, n (%)	3 (20)	25 (63)
Race, n (%)[a]		
White	13 (93)	36 (90)
Black	1 (7)	1 (3)
Asian	0	3 (8)
KRAS mutation, n (%)	–	23 (58)
Median no. prior regimens (range)	–	3.0 (1–11)
Prior systemic therapy, n (%)	–	39 (98)
Prior radiation therapy, n (%)	–	13 (33)
Prior surgery, n (%)	–	31 (78)

[a]Race not available for one patient in the escalation phase.

Safety

- Safety profile of durvalumab plus monalizumab combination is similar to monotherapy profiles
- Dose escalation completed with no DLTs; MTD not reached
- AEs in the MSS-CRC expansion cohort (**Table 2**)
  - The most common AEs were abdominal pain, decreased appetite, pyrexia, and vomiting
  - The most common treatment-related AEs were arthralgia, AST increased, hypothyroidism, pruritus, and rash
  - Three patients experienced treatment-related grade 3/4 AEs
    - SAE (grade 4 sepsis), resolved
    - Grade 3 AST increased, ongoing 3 days when patient withdrew from study
    - Grade 3 lipase increased, resolved
  - No fatal AEs or AEs leading to treatment discontinuation were reported

Table 2. Safety Summary (MSS-CRC Expansion Cohort)

Patients With AEs, Preferred Term	MSS-CRC Expansion (n=40)
≥ 1 AE	37 (92.5%)
Abdominal pain	10 (25.0%)
Decreased appetite	7 (17.5%)
Pyrexia	7 (17.5%)
Vomiting	7 (17.5%)
≥ 1 treatment-related AE	22 (55.0%)
Arthralgia	3 (7.5%)
AST increased	3 (7.5%)
Hypothyroidism	3 (7.5%)
Pruritus	3 (7.5%)
Rash	3 (7.5%)
≥ 1 grade 3/4 or SAE	13 (32.5%)
≥ 1 treatment-related SAE	1 (2.5%)
≥ 1 treatment-related grade 3/4 AE	3 (7.5%)
Fatal AE	0
≥ 1 AE leading to discontinuation of monalizumab and/or durvalumab	0

AE, adverse event; SAE, serious adverse event.

Clinical Activity

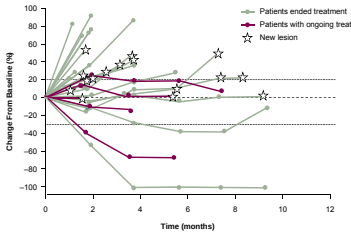
- Changes in tumor size for MSS-CRC patients and duration of treatment are shown in **Figures 3** and **4**
- In MSS-CRC expansion, there were 3 confirmed partial responses (PRs) and 11 patients with stable disease (SD), including 3 patients with tumor reduction who continued therapy for >200 days (**Table 3**)
- 8 patients (20%) had initial tumor reduction

Table 3. Clinical Activity in the MSS-CRC Cohort, Response Evaluable Population[a]

Parameter	MSS-CRC (n=39)
Best overall response, n (%)	
CR	0
PR	3 (8)[b]
SD	11 (28)
PD	22 (56)
NE/NA[c]	3 (8)
Overall response rate, n (%) [95% CI]	3 (8%) [2–22]
Median duration of response, weeks (95% CI)	16.1 (15.9–NE)
Disease control rate at 16 weeks, n (%) [95% CI]	12 (31) [17–48]

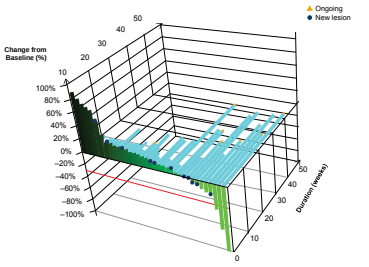
[a]Response evaluable population includes patients in the as-treated population who have at least 1 post-baseline disease assessment or discontinued due to death or disease progression prior to the first post-baseline disease assessment.
[b]One confirmed PR has had further reduction and is currently an unconfirmed CR.
[c]Includes 1 patient who withdrew consent before the first post-baseline disease assessment, 1 patient with non-evaluable target lesions at post-baseline disease assessment, and 1 patient with clinical progressive disease who discontinued treatment before first post-baseline disease assessment.
CR, complete response; MSS-CRC, microsatellite-stable colorectal cancer; PD, progressive disease; PR, partial response; SD, stable disease; NE, not evaluable; NA, not available.

Figure 3. Change in Tumor Size in MSS-CRC Patients in the Expansion Phase



MSS-CRC, microsatellite-stable colorectal cancer; PR, partial response; PD-L1, programmed death ligand-1; SD, stable disease.

Figure 4. Percent Change in Tumor Size From Baseline and Duration of Treatment in the MSS-CRC Expansion Cohort



MSS-CRC, microsatellite-stable colorectal cancer; PR, partial response; PD-L1, programmed death ligand-1; SD, stable disease.

Conclusions

- In this first-in-human study evaluating the combination of monalizumab plus durvalumab, the dose escalation phase showed a manageable toxicity profile, with no DLTs
- Preliminary efficacy data show encouraging activity in patients with heavily pretreated MSS-CRC
- The dose exploration phase in patients with CRC is ongoing
- Monalizumab is also being investigated in combination with cetuximab in patients with previously treated recurrent or metastatic head and neck squamous cell carcinoma (NCT02643550)[5]

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Disclosures

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